COMMENTS

Claims 29-48, 54, and 62 are pending and under examination in the present case. Claims 39, 40, and 54 have been cancelled herein without prejudice or disclaimer. Claims 29-32, 34-38, 41-42, 44-46, 48, 54, and 62 have been amended. Claims 63-68 have been added. Upon entry of this amendment, claims 29-38, 41-48, and 62-68 will be pending. Entry of the amendments and reconsideration of the application in view of the amendments herein is respectfully requested.

No new matter is added with the amendments to the specification and claims. Various paragraphs of the specification were amended to include full names to clarify abbreviations and to eliminate hypertext links. The amendments to claims 29, 34, 35, 41, 44, and newly added claim 67 that add specifically recited hybridization conditions are supported by page 5, last paragraph. The amendment to claim 29 indicating that the nucleic acid molecule encodes a polypeptide that has two double paired zinc finger motifs is supported by page 4, last paragraph. The amendment to claim 32 that indicates that the mammalian homolog hybridizes under low stringency conditions is supported by page 6, last paragraph to page 7, first paragraph.

Newly added claim 65 and the amendment to claim 32 that indicates that the nucleic acid molecule is identical in nucleotide sequence to a portion of human chromosome 21q22.3 or a portion of a mammalian chromosome that shares conserved synteny with human chromosome 12q2.3 is supported by Examples 1 and 20. Newly added claims 63 and 67 are supported by Example 7, which discloses the intracellular localization of the APGD1 protein. Newly added claim 64, which recites a nucleic acid molecule that co-segregates in a mutated form with Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED), is supported for example, by Example 1. Newly added claim 66, which recites that the substitution is a cytosine to thymidine exchange at nucleotide position 889, is supported for example, by Table 1, on page 40, which indicates that this mutation is the major mutation among the population of Finland. The remaining amendments to the claims correct typographical and/or obvious errors.

Objections to the Specification/Claims

The disclosure stands objected to because it allegedly does not include an abstract. Applicants respectfully traverse the rejection. Page 49 of the application as filed includes an Abstract. Therefore, Applicants respectfully request that the objection be withdrawn.

The disclosure stands objected to because various abbreviations are not spelled out in their first occurrence. Applicants traverse the objection. Regarding "TIF1," this abbreviation is indicated as Transcription Intermediary Factor 1 (TIF1) on page 5, lines 3-4 of the specification as filed. The other abbreviations cited in the Office Action are spelled out in their first instance in the amendments.

Various other typographical errors asserted in the Office Action have been corrected. The word "AIRE" has been inserted between "human" and "in a series" on page 23, line 1. Hyperlinks have been reworded to eliminate the hyperlink. An "a" has been inserted in claim 29. Claim 34 is amended herein to include a sequence identifier.

Claim 44 stands rejected as being dependent from a multiple dependent claim. The multiple dependence in claim 44 has been removed.

Claim Rejection under 35 U.S.C. § 101

Claims 29-48, 54, and 62 stand rejected under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter as not sufficiently distinguishing over naturally occurring biomolecules. Claim 54 is cancelled herein, thereby rendering the rejection moot with respect to this claim. Claims 29-48, and 62 are amended herein to include the term "isolated." Therefore, the rejection has been overcome and Applicants request withdrawal of the rejection of claims 29-48, 54, and 62 under 35 U.S.C. § 101.

Claim Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 29-48 and 54 stand rejected under 35 U.S.C. § 112, first Paragraph as containing subject matter which was not described by the disclosure in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. The Applicants respectfully traverse the rejection.

The Office Action acknowledges that the Applicants are in possession of the polynucleotide of SEQ ID NO:1 and a method of producing a polypeptide that is encoded by SEQ ID NO:1. However, the Office Action alleges that the Applicants were not in possession, as of the filing date, of nucleotides that fall within the entire scope of the claims. The Office Action asserts that the claims encompass a large number of polynucleotide variants that are both structurally and functionally deviated from SEQ ID NO:1. The Office Action further asserts that making changes from subs-sequences comprising as few as 14 nucleotides to the full-length SEQ ID NO:1 sequence does not provide maintaining the same three-dimensional structure of the polypeptide encoded by the polynucleotide of SEQ ID NO:1.

To expedite issuance of the present application and without prejudice or disclaimer, Applicants have canceled claim 54, thereby rendering moot, rejections related to this pharmaceutical composition claim. Furthermore, to expedite issuance of the present application and without prejudice or disclaimer, the pending claims as amended, do not make reference to gain or loss of function.

Claim 29 as amended recites that the nucleic acid molecule encodes a polypeptide with two double paired zinc finger motifs, such as SEQ ID NO:2, or a nucleic acid that hybridizes with a nucleic acid encoding SEQ ID NO:2 in a hybridization solution comprising 50% formamide, 6X SSC, 0.1% SDS, and 100ug/ml single-stranded DNA and a wash solution comprising 0.1x SSC, 0.1% SDS wherein hybridization is performed at a temperature above 37C and washing is performed at a temperature above 55C (Page 5, last paragraph). The disclosure identifies numerous sequence that fall within this claim. For example, the specification discloses SEQ ID NO:1 and polymorphic versions of SEQ ID NO:1, including those with silent C to T substitutions at positions 708, 801,1317, and 1698 (Fig. 2A, pg. 25,

first full paragraph) as well as other natural variants (Table 1). Furthermore, claim 29 as amended recites specific hybridization conditions that help to clarify the metes and bounds of nucleic acid molecules that fall within the claimed invention. Finally, claim 29 recites that the nucleic acid molecule encodes a polypeptide with two double paired zinc finger motifs, thereby assuring that the nucleic acid molecules encode a polypeptide that retains three-dimensional structural motifs of full-length SEQ ID NO:2. Therefore, the nucleic acid molecule of claim 1 is fully supported by the disclosure as filed.

Regarding claim 30, the Office Action alleges that Applicants are not in possession of a nucleic acid molecule having a function as a transcription factor because allegedly there is insufficient teaching, guidance and/or working examples. Applicants respectfully assert that the specification provides evidence to support the conclusion that nucleic acid molecules of the present invention can function as transcription factors. For example, the disclosure teaches that nucleic acid molecules of the present invention encode polypeptides having Cys4-His-Cys3 double-paired finger motifs, which are known to be found in nuclear proteins involved in the mediation or regulation of transcription (page 5, first paragraph). Furthermore, the disclosure as filed reveals the nuclear localization of the APGD1 protein (Example 11) and recognizes the function of the protein as a transcription factor (See claim 2 as filed). Finally, the function of the encoded APGD1 protein in the mediation or regulation of transcription is further substantiated by literature published after the filing date of the present application (See e.g., Pitkanen et al., *J. Biol. Chem.*, 276, 19597 (2001) (teaching that AIRE activates the IFNB minimal promoter) (Exhibit A)).

Regarding claim 32 directed at mammalian homologs, the Office Action asserts that the claim covers a genus encompassing numerous analogs or derivatives of the claimed polynucleotides. The Office Action alleges that the specification provides insufficient description in this regard, asserting that the applicants are not in possession of any mammalian homolog to human SEQ ID NO:1. Claim 32 as amended, is directed at a mammalian homolog that is complementary to a nucleic acid that hybridizes to SEQ ID NO:1 or SEQ ID NO:6 under low stringency conditions, and which is identical in sequence to a portion of human

chromosome 21q22.3, or a portion of a mammalian chromosome that shares conserved synteny with human chromosome 21q22.3. Therefore, claim 32 as amended clarifies the structural properties of the claimed, isolated nucleic acids.

The specification discloses a sufficient number of exemplary nucleic acid molecules that fall within the claimed genus to meet the written description requirement with respect to claim 32. For example, the specification provides SEQ ID NO:1, the sequence of a portion of the human APGD1 (also referred to as AIRE) gene including the coding sequence. Furthermore, the specification provides the sequence of five different naturally-occurring human APGD1 mutant and/or polymorphic versions that fall within the claim (Example 3). Finally, the specification provides the sequence of SEQ ID NO:6, the mouse APGD1 coding sequence (Example 19), and localizes the mouse APGD1 sequences to chromosome 10, a mouse chromosome that shares conserved synteny with human chromosome 21q22.3. Therefore, contrary to the assertions in the Office Action, the specification provides numerous mammalian nucleic acid molecules that fall within claim 32 and provides sufficient disclosure to support amended claim 32. Furthermore, it is noteworthy that claims 33 and 34 are even more clearly supported by the disclosure as filed because they are directed specifically at a murine homolog (claim 33) and the specific murine homolog isolated in the specification (claim 34) (Example 19).

Regarding claim 35, which is directed at insertions, deletions, substitutions, or inversions, the Office Action asserts that the claim encompasses all possible mutations which can be produced either via *in vitro* mutagenesis or via genetics, without regard to structure-function relationship. This allegedly would create numerous unpredictable variants and mutants and would require undue experimentation. Amended claim 35 is not directed at *all* possible mutations of human APGD1 nucleic acids (SEQ ID NO:1). Rather, claim 35 recites structural and functional elements that further define mutated versions of SEQ IN NO:1 that fall within the claimed invention. For example, claim 35 specifies that the claimed nucleic acid hybridizes to SEQ ID NO:1 in a hybridization solution comprising 50% formamide, 6X SSC, 0.1% SDS, and 100ug/ml single-stranded DNA and a wash solution comprising 0.1x SSC,

0.1% SDS wherein hybridization is performed at a temperature above 37C and washing is performed at a temperature above 55C. Furthermore, claim 35 recites that the nucleic acid molecule is identical in nucleotide sequence to a mutated nucleic acid that co-segregates with APECED.

Further evidence that the specification meets the requirements of 35 U.S.C. 112, first paragraph with respect to claim 35 is provided by the identification and isolation of numerous nucleic acids that fall within claim 35. More specifically, the specification reports the isolation of 5 mutations in APGD1 that co-segregate with APECED and that fall within claim 35 (See Table 1, pg. 40). Furthermore, claims 36-38 recite specific mutations that are identified in the specification as filed.

Regarding claims 41-44, as amended these claims clarify that the nucleic acid fragment or primer pair, respectively, hybridizes to SEQ ID NO:1 in a hybridization solution comprising 50% formamide, 6X SSC, 0.1% SDS, and 100ug/ml single-stranded DNA and a wash solution comprising 0.1x SSC, 0.1% SDS wherein hybridization is performed at a temperature above 37C and washing is performed at a temperature above 55C. Such fragments or primer pairs are useful for example, as probes or amplification primers for the APGD1 nucleic acids of the present invention, such as for SEQ ID NO:1. Therefore, information regarding a polypeptide encoded by the fragments or primer pairs is not necessary to meet the requirements of 35 U.S.C. § 112, first paragraph for these claims, as alleged in the Office Action (See Office Action page 7, lines 6-8).

In summary, Applicants respectfully assert that the specification meets the written description requirement of 35 U.S.C. § 112, first Paragraph with respect to claims 29-48 and 54. Therefore, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Claim Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 29-48, 54 and 62 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. Applicants respectfully traverse the rejection.

The Office Action alleges that the phrases "a portion" and "hybridizing" in claim 29 render the claim indefinite. The phrase "a portion" has been deleted from claim 29. Furthermore, specific hybridization conditions are recited in claim 29 as amended.

The Office Action alleges that the phrase "function of transcription factor" renders claim 30 indefinite. Claim 30 as amended clarifies that the polypeptide modulates or regulates transcription. This function is well known. Therefore, claim 30, as amended is defined.

The Office Action alleges that the phrase "double-paired zinc finger motifs" renders claim 31 indefinite, asserting that the recitation is unclear and not defined in the specification. Furthermore, the Office Action alleges that it is unclear whether the term "double" modifies "paired" or "paired zinc finger motifs." The specification clarifies that the APGD1 protein includes two double-paired finger motifs (Page 4, last paragraph). A skilled artisan will understand that the protein includes two copies of a motif called a "double-paired finger motif." Furthermore, specific nucleotide sequence patterns of the two, paired zinc finger motifs as well as the identification of other paired zinc finger motif-containing proteins are provided in the specification (Page 4, last paragraph to page 5, first paragraph) Accordingly, Applicants traverse the rejection.

The Office Action alleges that claim 34 is indefinite because it references figure 14. Claim 34 as amended does not refer to figure 14. Therefore, the rejection has been overcome.

The Office Action alleges that the term "deviating" renders claim 35 indefinite. Claim 35 as amended does not include this term. Therefore, the rejection has been overcome.

The Office Action alleges that the terms "and/or" and "a loss of function or a gain of function" renders claim 35 indefinite. Claim 35 as amended does not include either of these phrases. Therefore, the rejection has been overcome.

The Office Action alleges that claim 37 is indefinite because it is allegedly not clear whether nucleotides 1085-1097 are consecutive in the sequence. Applicants traverse the rejection. Claim 37 is directed at a nucleic acid molecule that differs from SEQ ID NO:1 by the recited differences, including, for example a 13 nucleotide deletion of nucleotides 1085-1097. A skilled artisan will recognize from the nucleotide numbering that 13 consecutive nucleotides are deleted. Therefore, the rejection of claim 37 regarding nucleotides 1085-1097 is traversed.

The Office Action alleges that claim 48 is indefinite because it is multiply dependent. As amended claim 48 depends only from claim 29. Therefore, the rejection of claim 48 has been overcome.

In summary, Applicants assert that claims 29-48, 54, and 62 are definite. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Claim Rejection Under 35 U.S.C. § 102

Claims 29, 32, 34-35, 41, 43, 45-47, and 54 stand rejected under 35 U.S.C. § 102 as being anticipated by Klinger et al. (U.S. Pat. No. 6,071,717). Applicants respectfully traverse the rejection. The Office Action alleges that nucleotides 1535-1564 of SEQ ID NO:2 of Klinger et al., is complementary to the nucleotide sequence from nucleotides 2089-2118 of SEQ ID NO:1 of the present application. The Office Action alleges that this teaching anticipates claim 29, item c, claim 34, item c, claim 35, item c, and claims 32, 41, and 43. Furthermore, the Office Action alleges that Klinger et al. teach vectors, hosts, and therapeutic compositions, thereby allegedly anticipating claims 32, 45-47, and 54.

To anticipate an invention, every element of a claim must be found in a single prior art reference. MPEP § 2131; Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628,631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Claim 29 as amended recites that the isolated nucleic acid molecule includes two double paired zinc finger motifs. Klinger et al. is silent as to a

nucleic acid molecule encoding a protein with these motifs. Therefore, Klinger et al. does not anticipate claim 29 or claims dependent therefrom.

Claim 35 recites that the claimed nucleic acid molecule is identical in nucleotide sequence to a mutated nucleic acid that cosegregates with APECED. As disclosed in the present disclosure, mutations of the APGD1 gene represent the primary cause for the APECED disease (Page 26, last paragraph). Furthermore, the present specification discloses that APGD1 is located on chromosomal location 21q22.3 (Example 1). Klinger et al. is silent as to a nucleic acid molecule that cosegregates with APECED. Rather, Klinger et al. teach the PKD1 gene located on chromosome location 16q13.3 (Klinger et al., Col. 5, lines14-16), mutations of which apparently relate to adult-onset polycystic kidney disease, not APECED. Therefore, Klinger et al. does not anticipate claim 35, or claims dependent therefrom.

Finally, claims 29 and 35, from which the remaining claims included in this rejection depend, recite that the nucleic acid molecule hybridizes to SEQ ID NO:1 in a hybridization solution that includes 50% formamide, 6X SSC, 0.1% SDS, and 100ug/ml single-stranded DNA and a wash solution comprising 0.1x SSC, 0.1% SDS wherein hybridization is performed at a temperature above 37C and washing is performed at a temperature above 55C. SEQ ID NO:2 of Klinger et al. is a 53,526 nucleic acid molecule. SEQ ID NO:1 of the present invention is a 2245 nucleotide sequence. The Office Action alleges that claims 29, 32, 34-35, 41, 43, 45-47, and 54 are anticipated by a 30 nucleotide stretch of the 53,526 nucleotide SEQ ID NO:2 of Klinger et al. that allegedly is complementary to a portion of SEQ ID NO:1 of the present specification. Given the short length of this sequence complementarity relative to the size of these nucleic acid molecules, a skilled artisan would recognize that SEQ ID NO:2 of Klinger et al. would not hybridize to SEQ ID NO:1 under the recited conditions.

In summary, Klinger et al. does not anticipate the present invention because it is silent as to one or more elements of claims 29 and 35, from which the remaining rejected claims depend. For example, Klinger et al. is silent regarding a nucleic acid molecule that encodes a polypeptide with two double paired zinc finger motifs, is silent regarding a nucleic acid

molecule that cosegregates with APECED, and is silent regarding a nucleic acid molecule that hybridizes to the nucleic acid molecules of the present invention under the recited conditions. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 29, 32, 34-35, 41, 43, 45-47, and 54 under 35 U.S.C. § 102 as being anticipated by Klinger et al. (U.S. Pat. No. 6,071,717).

Claim Rejection Under 35 U.S.C. § 103(a)

Claims 29, 32, 34, 35, 41-48, 54, and 62 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious in view of Aaltonen, J. et al. (*Genome Res.*, 7:820-829 (August 1997)) taken with Bjorses, P. et al. (*Am. J. Hum. Genet.* 59:879-86 (1996)) and Korenberg, J. R., et al. (U.S. Pat. No. 6,166,180). Applicants respectfully traverse the rejection.

The Office Action alleges that Aaltonen et al. teach localization of an APECED gene in a 800 kb region of human chromosome 21q22.3 using fiber fluorescent *in situ* hybridization (FISH) and primers for this gene. Furthermore, the Office Action alleges that Bjorses et al. teach localization of an APECED gene in human chromosome 21q22.3 using linkage and haplotype analysis, and suggest use of positional cloning to isolate the gene responsible for APECED. The Office Action alleges that the combination of Bjorses et al.'s suggestion to use positional cloning with Aaltonen et al.'s use of positional cloning and FISH, would lead to the invention of the rejected claims. Furthermore, the Office Action alleges that Korenberg et al. teach a gene marker located on 21q22.3 as well as vectors, hosts, and methods for producing proteins encoded by a polynucleotide.

To establish a *prima facie* case of obviousness there must be some suggestion or motivation in the prior art to make the claimed invention, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim limitations. MPEP § 2142; In re Vaeck, 947 F.2d 488, 20 USPQ2d, 1438 (Fed. Cir. 1991). The Federal Circuit clarified requirements related to obviousness rejections of claims directed at nucleic acid molecules in In re Deuel (34 USPQ2d, 1210 (Fed. Cir. 1995)), affirming its prior decision of In re Bell (26 USPQ2d, 1529 (Fed. Cir. 1993)). The Federal Circuit in In re Deuel

held that nucleic acid claims directed at nucleic acid molecules that encode human heparin-binding growth factors (HPGFs) were not rendered obvious by prior art teaching of the isolation of human HBGFs and the disclosure of a portion of their amino acid sequence, combined with known methods of using protein sequences to synthesize primers for cloning nucleic acid molecules encoding the protein. In re Deuel, at 1215. The Federal Circuit in In re Deuel indicated that since the claims at issue claimed new chemical entities in structural terms, "a *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds*" (emphasis in original). Id., at 1214. The court further concluded that while the general idea of the claimed molecules, their function, and their general chemical nature may have been obvious from Bohlen's teachings, and the knowledge that some gene existed may have been clear, the precise cDNA molecules of the claims would not have been obvious. Id., at 1215.

As impliedly acknowledged in the Office Action, the primary reference cited in the Office Action, Aaltonen et al., does not disclose a nucleic acid molecule that encodes SEQ ID NO:2, or that hybridizes with a nucleic acid molecule that encodes SEQ ID NO:2 under the recited conditions of claims 29 and 35, from which the remaining rejected claims depend. Aaltonen et al. use FISH to map the APECED locus on chromosome 21q22.3. Aaltonen et al. indicate that they provide "the tools" for the cloning of the APECED gene (Aaltonen et al., pg. 826, right column, last paragraph before Methods section), and emphasize that the gene responsible for APECED lies in a chromosomal region that is difficult to clone (pg. 826, left col., second full paragraph). Aaltonen et al. do not teach information related to the chemical structure (i.e. the nucleotide sequence) of the nucleic acid molecules of claims 29 and 35.

Similarly, the secondary references, Bjorses et al. and Korenberg et al. are also silent regarding structural features of a nucleic acid molecule of claims 29 or 35. Bjorses et al. perform linkage analysis in Finnish and Iranian Jewish APECED patients, to conclude that APECED is likely the result of a spectrum of mutations of a gene on chromosome 21. Bjorses et al. point out that the gene is "still unknown" (Abstract, last sentence) and indicate that "[m]ost likely, APECED represents a novel gene locus, which *will have to be* isolated by

positional cloning" (emphasis added). Therefore, Bjorses et al. does not provide structural information regarding the claimed nucleic acid molecules.

Korenberg et al. fail to provide the missing structural information of Aaltonen et al. and Bjorses et al. The Office Action does not allege that Korenberg et al. teach this information. Rather, as indicated above, the Office Action alleges only that Korenberg et al. teach vectors and hosts. Korenberg et al. teach the amino acid sequence of an unrelated protein, EHOC-1. Therefore, Korenberg et al. do not provide teachings regarding the structure of the nucleic acid molecule of pending claims 29 and 35 to overcome the deficiency of Aaltonen et al. and Bjorses et al. Therefore, similar to the factual situation in In re Deuel, the Office Action asserts prior art that teaches methods that allegedly would assist in the identification of a nucleic acid molecule of the pending claims, but does not provide information regarding the structure of the claimed nucleic acid molecules. Accordingly, the Office Action fails to state a *prima facie* case of obviousness.

The patentability of the inventions of the pending claims over the cited references is further established for dependent claims 36, 37, 38, and 62. These claims are directed at nucleic acid molecules with specific, recited nucleotide sequences. The cited art doest not provide information regarding these nucleotide sequences. Therefore, the cited art does not render these claims obvious.

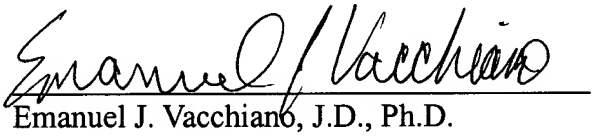
In summary, the Office Action fails to state a *prima facie* case of obviousness for claims 29 and 35, or claims dependent therefrom. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 29, 32, 34, 35, 41-48, 54, and 62 under 35 U.S.C. § 103(a) as allegedly being obvious in view of Aaltonen, J. et al., taken with Bjorses, P. et al. and Korenberg, J. R., et al.

If the Examiner believes that a telephonic or personal interview would be helpful to terminate any issues which may remain in the prosecution of the Application, the Examiner is requested to telephone Applicants' attorney at the telephone number set forth herein below.

The Commissioner is hereby authorized to charge any additional fees which may be required in the Application to Deposit Account No. 50-1355.

Respectfully submitted,

Date: September 16, 2003



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